REMARKS

In the Claims:

Claims 15-24 are pending in this case. Claim 24 has been withdrawn from consideration as to a non-elected species.

Specification

The Examiner maintained the objection to the specification because application 08/485,355, now U.S. Patent No. 6,177,075, was identified as a continuation in part, rather than a continuation, of application 08/440,522. Applicant asserts that 08/485,355 is as a continuation in part, not a continuation, of application 08/440,522. This fact is properly reflected on the first page of U.S. Patent No. 6,177,075.

The Examiner objected to the specification for presence of a typographical error on page 11. Applicant has amended the specification to replace the term "later" with the term --larger-- on line 17 of page 11, thus addressing the rejection.

Claim Rejections – 35 U.S.C. §112, First Paragraph, Written Description

Claim 15 (and Claims 16-19, 21and 22 which depend therefrom) remains rejected under 35 U.S.C. §112, first paragraph, on the grounds that the written description fails to describe the invention in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time of filing. The Examiner cites Amgen v. Chugai and University of California v. Eli Lilly for the principle that an applicant must provide more than a statement of the biological function of the DNA in order to satisfy the written description requirement. The Examiner states that the Applicant must identify some structural characteristic of the claimed nucleic acids that distinguish these nucleic acids from other nucleic acids in order

to support the claims. However, the holdings in Amgen and Lilly are directed toward situations in which the applicant is attempting to claim the nucleic acid that encodes a protein identified by a specific function. In contrast, present invention is directed to a nucleic acid encoding at least one capsid protein of an insect small RNA virus and a second sequence which is insecticidal or which encodes an insecticidal protein toxin. Thus, the invention is directed toward, for example, an assembled capsid, comprising one or more of the capsid protein. These assembled virus capsids are useful as vectors for insecticidal agents. As such the assembled viral capsids may be used to administer insecticidal agents such as various nucleotide sequences with insecticidal activity or various toxins to an insect. Nucleotide sequences in the form of RNA or DNA which can be used include those of the HaSV genome or other insect viruses. Toxins which can be used advantageously include those which are active intracellularly and may also include neurotoxins with an appropriate transportation mechanism to reach the insect neurones. The invention, therefore, is that of providing a first nucleic acid encoding the capsid and a second nucleic acid transported along with and protected by the capsid.

As described in the specification, when the first sequence is expressed, it produces virus-like particles able to transport the nucleic acids of the second sequence or the toxin encoded by it across the gut barrier into cells of an insect. This is achieved because 1) the capsid protein encoded by the first sequence is resistant to degradation in the formidable environment of an insect's gut, and ii) the capsid protein also targets the insect gut cell thus delivering the nucleic acid of the second sequence or the protein toxin into the cell. Accordingly, the first sequence functions to deliver the second sequence or its expression product into an insect cell.

As set forth in the specification and in the references cited therein, the nucleic acid sequence or sequences incorporated into the recombinant vector may be a cDNA, DNA or DNA sequence and may comprise the genome or portion thereof of a DNA or RNA of HaSV or another species. Suitable nucleic acid sequences for incorporation into the recombinant vector include insecticidally effective agents such as a neurotoxin from the mite Pyemotes tritici (Tomalski, M. D. & Miller, L. K. Nature 352, 82-85 (1991) a toxin component of the venom of

the North African scorpion Androctonus australia Maeda, S. et al. Virology 184-777-780 (1991) Stewart, L. M. D. et al., Nature 352, 85-88 (1991), Conotoxins from the venom of Conus spp. (Olivera B. M. et al., Science 249, 257-263 (1990); Woodward S. R. et al., EMBO J. 9, 1015-1020 (1990); Olivera B. M. et al., Eur. J. Biochem. 202, 589-595 (1991). [Specification, page 19-20].

The specification provides further discloses that the viral capsids may be used to administer insecticidal agents such as various nucleotide sequences with insecticidal activity or various toxins to an insect. Nucleotide sequences in the form of RNA or DNA which can be used include those of the HaSV genome or other insect viruses. Toxins which can be used advantageously include those which are active intracellularly and may also include neurotoxins with an appropriate transportation mechanism to reach the insect neurones. [Specification page 20, lines 21-30]

Additional examples of toxins disclosed in the specification that may be encoded by the second nucleic acid sequence include, Bacillus thuringiensis d-toxin, insect neurohormones, insecticidal compounds form wasp or scorpion venom or of heterologous origin, or factors designed to attack and kill infected cells in such a way so as to cause pathogenesis in the infected tissue (for example, a ribozyme targeted against an essential cellular function). Furthermore, the specification sets forth that nucleic acid constructs may also be provided which include mechanisms for regulating pathogen expression (for example, mechanisms which restrict the expression of ribozymes to the insect cells) by tying for example, expression to abundant virus replication, production of minus-strand RNA or sub-genomic mRNA's; and/or mechanisms similar to, or analogous to, those described in copending International patent application number PCT/AU92/00413 so as to achieve a limited-spread system (such as control of replication).

Example 12 of the specification provides a detailed discussion of the types of nucleic acids and toxins encoded by the nucleic acids that may be used in the invention. The examples given provide a solid sampling of the possible toxins that may be used, but are not to taken as a complete listing.

One of skill in the art reading the specification would have understood that that Applicant had possession of the present invention at the time of filing. The specification clearly sets forth numerous examples of possible insecticidal sequences that could be used in conjunction with a nucleic acid molecule encoding at least one capsid protein of an insect small RNA virus for delivery into an insect cell.

Additionally, the specification provides adequate guidance that one of skill in art would recognize that the invention could be used to deliver any number of other nucleic acids of interest into a cell in the gut of an insect for expression, or insecticidal function, therein. For the foregoing reasons, the specification provides adequate descriptions of the insecticidal and antisense sequences recited in the claims. Applicant accordingly respectfully requests withdrawal of the outstanding rejection of Claims 15 (and Claims 16-19, 21and 22 which depend therefrom) under 35 U.S.C. §112, first paragraph.

Claim Rejections – 35 U.S.C. §112, First Paragraph, Enablement

Claim 15-19 and 21-23 are rejected under 35 U.S.C. §112, first paragraph, for lacking enablement. In particular, the Examiner states that the specification does not reasonably provide enablement for the claimed nucleic acids where the second sequence is any ribozyme, antisense, or other insecticidal nucleic acid. Claim 20 was not subject to the rejection because it recites a specific insecticidal toxin. The Examiner asserts that the specification does not provide sufficient guidance to use the invention with any insecticidal nucleic acid or than the specific disclosed embodiments.

As discussed in the Written Description section above, the present invention is directed to a nucleic acid molecule comprising a first sequence encoding at least one capsid protein of an insect small RNA virus that can be used to deliver a second nucleic acid sequence or the toxic protein encoded by it to an insect cell. One of skill in the art would recognize that the invention

may be used to deliver a nucleic acid of interest or toxin into an insect cell. The specific identities of the nucleic acids need not be determined until the invention is to be used.

As set forth in the written description section above, the specification provides numerous examples of nucleic acids or toxins encoded by the nucleic acids that may be used in the invention.

The Examiner discusses the difficulty in delivering biologically active oligonucleotides to a cell. This difficulty is precisely the problem that is addressed by the present invention. The first sequence recited in Claim 15 encodes at least one capsid protein of an insect small RNA virus and serves as a vector for delivering a second sequence or toxin.

Furthermore, the skilled artisan is aware that ribozymes are catalytic forms of antisense sequences. Both antisense sequences and ribozymes hybridize to target mRNA molecules for the inhibition of gene expression. Ribozymes, in addition to binding target mRNA, directly cleave ribonucleic acid. Accordingly, the nucleic acids recited in the claims (e.g., having a second sequence encoding an "antisense sequence") can readily be produced by the skilled artisan without undue experimentation. As indicated herein, the nucleic acids of the present invention may be used to deliver any functional nucleic acid (e.g., a nucleic acid sequence which is insecticidal *per se* or a nucleic acid which encodes an insecticidal toxin), to an insect host. The construction of nucleic acids in which the second sequence is an antisense sequence is, moreover, provided in the specification and in the Examples (e.g., see page 82, lines 20-30). The specification further provides that selected genes may be placed under the control of *Helicovera armigera* replication or encapsidation signals using standard techniques in molecular biology (see e.g., page 83, lines 1-5 and 29-31 and page 84, lines 1-2) . Given the present disclosure, the skilled artisan can readily appreciate that any selected nucleic acid (e.g., antisense or otherwise) can be delivered to an insect host using the nucleic acid molecule that is recited in claim 15.

The Examiner is concerned with the non-specific toxic effects, and difficulties in treating disease that may arise from use of antisense administration. The Applicant respectfully points

out the present invention is drawn toward insecticidal nucleic acids, as such is not concerned with unwanted toxic effects or treatment of a diseased patient.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech Inc. v. Monoclonal Antibodies, Inc. 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463 221 USPQ 481, 489 (Fed. Cir. 1984).

Applicant maintains that this burden has been met and accordingly requests withdrawal of the outstanding enablement rejection under 35 U.S.C. §112, first paragraph.

Claim Rejections – 35 U.S.C. §103(a) – *Wilcox, et al.* in view of *Harley, et al.*

Claim 15 (and claims 16 and 19-23 which depend therefrom) is rejected under 35 U.S.C. §103(a) as being anticipated by *Wilcox, et al.* in view of *Harley, et al.* Applicant respectfully disagrees with the rejection for the reasons below.

The present invention is directed to an isolated nucleic acid molecule comprising a first sequence encoding at least one capsid protein of an insect small RNA virus and a second sequence which is insecticidal or which encodes an insecticidal protein toxin. Applicant asserts that the invention is not obvious over the cited references.

To establish a *prima facie* case of obviousness under 35 U.S.C.§103, the Examiner must demonstrate that, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. Further, the prior art must provide one of ordinary skill with a reasonable expectation of success. M.P.E.P. §2143.

Wilcox, et al. teaches insecticidal fusion proteins expressed as polypeptide products of a hybrid gene comprising a cytoxic agent (*e.g.*, a ribosome inactivator such as ricin) and a specific

insect gut cell recognition ("binding") protein wherein the gut cell recognition protein directs the cytotoxic agents to the host targets (*see e.g.*, column 1, lines 44-49 and column 3, line 27). However, the protein capsovector is distinct from immunotoxins, such as described in *Wilcox*, in that its structure also protects the toxin moiety from degradation in addition to binding to the midgut cell. The toxin fragment will be contained within the capsid shell until the capsovector enters the midgut cell. There is no teaching in *Wilcox* regarding the use of nucleic acids encoding capsid proteins to produce the immunotoxins of *Wilcox*.

Harley, et al merely relates to the identification of three viruses which infect *Helicoverpa armigera*. *Harley* generally describes the genomic structure of these viruses but makes no mention of the potential use of the nucleic acid encoding the capsid protein as a means for delivering an insecticidal sequence to an insect cell. The fact that the one of the viruses disclosed in *Harley* was located in the gut of an bollworm does not necessarily indicate that the virus was targeted only to the gut. Furthermore, there is no mention in *Harley* of using a nucleic acid encoding a capsid protein to direct a second nucleic acid sequence to the gut of an insect.

The references, when taken together, do not teach all aspects of the present invention. As noted by the Examiner, *Wilcox* does not teach the insect gut recognition as derived from a capsid protein of an insect small RNA virus. *Harley* does not make up for this deficiency. *Harley* does not disclose the use of the nucleic acid encoding the capsid protein for delivering an insecticidal sequence to an insect. Neither *Wilcox* nor *Harley* teach or suggest that a capsid protein of an insect small RNA virus can be used in a system of delivering an insecticidal sequence to an insect gut cell. It is the capacity of capsovectors to protect the toxin moiety from degradation in the midgut lumen that makes it distinct from other insect control factors that are fused to elements that only "interact" with midgut cells. Neither reference teaches this aspect of the invention.

The Examiner states that it would have been *prima facie* obvious to have incorporated one or more capsid proteins from the RNA virus described by *Harley* into the hybrid immunotoxin taught by *Wilcox* in order to arrive at the present invention. However, *Harley* does

not teach use of a capsid protein to target a virus to the gut and *Wilcox* does not teach a nucleic acid construct of the present invention but rather teaches an immunotoxin or fusion of an antigen-recognition moiety with a toxin.

Furthermore, there is no indication in either *Wilcox* or *Harley* that if one were to take the nucleic acid encoding a capsid protein of an insect small RNA virus and attach a second sequence that the second sequence would be successfully delivered into the gut of an insect cell where it could serve as an insecticidal nucleic acid or be translated into an insecticidal protein toxin. The Applicant reitierates that it is the capacity of capsovectors to protect the toxin moiety from degradation in the midgut lumen that makes it distinct from other insect control factors that are fused to elements that only "interact" with midgut cells. Neither reference teaches this aspect of the invention.

Accordingly, the Applicant asserts that claim 15 (and claims 16 and 19-23 which depend therefrom) are not obvious over the cited prior art.

CONCLUSION

Applicants submit that the claims are now in condition for allowance. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

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Appendix - Pending Claims

1-14. (canceled)

15. (original) An isolated nucleic acid molecule comprising a first sequence encoding at least one capsid protein of an insect small RNA virus and a second sequence which is insecticidal or which encodes an insecticidal protein toxin.

16. (original) An isolated nucleic acid molecule as claimed in claim 15 in which the nucleic acid is RNA.

17. (previously presented) An isolated nucleic acid molecule as claimed in claim 15 in which the insect small RNA virus is Helicoverpa armigera stunt virus (HaSV).

18. (previously presented) An isolated nucleic acid molecule as claimed in claim 15 in which the capsid protein is HaSV P71 (SEQ ID NO: 50).

19. (original) An isolated nucleic acid molecule as claimed in claim 15 in which the insecticidal toxin is of plant origin.

20. (original) An isolated nucleic acid molecule as claimed in claim 15 in which the insecticidal toxin is Ricin A.

21. (previously presented) An isolated nucleic acid molecule as claimed in claim 15 in which the second sequence is an antisense sequence or a ribozyme.

22. (previously presented) An isolated nucleic acid molecule as claimed in claim 21 in which the second sequence is double stranded RNA.

23. (original) An isolated nucleic acid molecule as claimed in claim 15 in which the insecticidal toxin is less toxic to plants than insects.

24. (withdrawn) A transgenic plant having introduced into its genome the nucleic acid of claim 15.

25-32. (canceled)